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10/049,306	06/05/2002	Antonino Cattaneo	6596	9842

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,306	CATTANEO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *20-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/11/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A preliminary amendment was received and entered on 2/11/02.

A response to a requirement for election/restriction was received and entered on 3/3/05. Applicant's election of group 1, claims 1-19 is acknowledged. Claims 20-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/3/05.

Claims 1-19 are under consideration in this Office Action.

Information Disclosure Statement

An information disclosure statement was received and entered on 2/11/02. Documents AD, AE, AI, AJ, AK, AL, and AN were considered, Document AM was not received. Applicant is advised that under 37 CFR 1.98, each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication. This has not been done for references AI-AN, consequently references AI-AN have not been initialed on the PTO-1449 received on 2/11/02. Appropriate correction is required.

Priority

This Application is the national phase of PCT/IT00/00321, filed in English on 7/28/00. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. These include MI99A001783, filed

8/6/99 and RMA000306 filed 6/5/2000. These documents are in the Italian language. Due to the availability of intervening art, a translation of each priority document is required, as per 35 USC 365(c).

Specification

The specification is objected to because it contains two copies of page 25.

The brief description of Fig. 1 is objected to because, although panels A-E are described, panel F is not.

The brief description of Fig. 16 is objected to because, although panels A, B, and D-F are described, panel C is not.

Appropriate correction is required.

Drawings

Figure 4 is objected to because although the brief description mentions panels A and B, the drawing is not labeled accordingly.

Figure 5(c) and Figure 6(c) are objected to because they are in the Italian language.

Fig. 27 is objected to because the photomicrographs are inverted relative to the Figure label. Note the inverted A and B in the lower left hand corners of each photo.

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because "trangenic" is misspelled.

Claims 4-6 are objected to because they lack a conjunction preceding the final member of each Markush group.

Claims 7-9 are objected to because claim 7 recites "as defined in Table 1." Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted). See MPEP 2173.05(s).

Claim 12 is objected to as ungrammatical. Deletion of "the" immediately before "adulthood" is suggested.

Claim 19 is objected to because "BS6JL" is misspelled. The 'S' and the '6' are transposed.

Appropriate correction is required.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to

comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 43, line 4 discloses an oligonucleotide 9 nucleotides in length that is not accompanied by a SEQ ID NO.** Applicant must provide:

An initial computer readable form (CRF) copy of the "Sequence Listing".

An initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4-10, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite because it is unclear what is intended by "atrophy/dystrophy". It is unclear if the claim requires the attributes of atrophy *and* dystrophy, or only one attribute of atrophy *or* dystrophy.

Claims 4-10 are indefinite because they recite "the tau protein" without antecedent basis. Deletion of 'the' is suggested.

Claim 9 is indefinite because it recites "the beta amyloid protein deposition in the back or lower limb skeletal muscles" without antecedent basis. Claim 9 also recites "said skeletal muscles" without proper antecedent basis. There are two antecedents for "said skeletal muscles". Table 1 refers to "skeletal muscles" generally at page 10, and claim 9 also recites lower limb skeletal muscles. It is unclear whether "said skeletal muscles" is limited to lower limb skeletal muscles, or whether it includes all skeletal muscles.

Claims 14 is indefinite because it recites "the monoclonal anti-NGF alphaD11 antibody" without proper antecedent basis. It is clear from the disclosure and claims that chimeric and non-chimeric versions of monoclonal anti-NGF alphaD11 antibodies exist. It is unclear to which of these versions the claim refers.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is broadly directed to any non-human transgenic animal that expresses a transgene encoding any antibody, or fragment thereof, and that has a phenotype that is reminiscent of any human pathology. Dependent claims add various limitations regarding phenotypic characteristics, identity of transgene, and species of animal.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by complete structure. It is not realistic to expect that the "complete structure" of a mouse, or any other animal could be described. Therefore the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described. In this case, the specification discloses a transgenic mouse that expresses an antibody against nerve growth factor (NGF). The mouse exhibits a variety of phenotypic characteristics affecting neural and muscular physiology. The specification does not disclose any mouse that expresses any other antibody, nor any mouse exhibiting symptoms

reminiscent of any of a wide variety of human pathologies such as for example, cancer, diseases of the heart, lungs, liver, kidneys, gastrointestinal tract, or reproductive tract, osteoporosis, HIV, influenza infection, or any disease not related to the central nervous system or muscles.

Next, it is to be determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. However, it is not possible to adequately describe the genus of claimed animals because the effects of expression of a heterologous gene can not be predicted. Without evidence to the contrary, transgene expression, or inhibition of gene expression, in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The specification has not clearly demonstrated or described a method to determine the empirical nature of genetics as it varies among species, in particular the ability of describing an animal resulting from the random insertion of a transgenic construct.

The Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov), state that in an unpredictable art adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. It follows that the disclosure of a single transgenic mouse expressing an anti-NGF antibody and having

neuromuscular defects would not convey to one of skill in the art that Applicant was in possession of the claimed genus at the time of the invention.

Scope of Enablement

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse that expresses transgenes encoding the heavy and light chains of an anti-NGF antibody, wherein the mouse has one or more of the following phenotypic characteristics: deposition in the central nervous system of plaques of amyloid precursor protein or beta amyloid protein, hyperphosphorylation of tau protein, neurofibrillary tangles, cortical atrophy, hippocampal atrophy, cerebral ventricle dilation, reduced number of forebrain cholinergic neurons, glial activation, skeletal muscle atrophy, amyloid precursor protein deposits in skeletal muscles, skeletal muscle inflammation, skeletal muscle vacuolization, and a spatial learning deficit, does not reasonably provide enablement for animals other than mice that are transgenic for an antibody and have a phenotype reminiscent of any other human pathology, or for animals that do not express an entire antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1 is broadly directed to any non-human transgenic animal that expresses a transgene encoding any antibody, or fragment thereof, and that has a phenotype that is

reminiscent of any human pathology. Dependent claims add various limitations regarding phenotypic characteristics, identity of transgene, and species of animal.

The specification discloses a transgenic mouse that expresses heavy and light chains of an antibody against nerve growth factor (NGF). The mouse exhibits a variety of phenotypic characteristics affecting neural and muscular physiology. The specification does not disclose any mouse that expresses any other antibody, nor any mouse exhibiting symptoms reminiscent of any of a wide variety of human pathologies such as for example, cancer, diseases of the heart, lungs, liver, kidneys, gastrointestinal tract, or reproductive tract, osteoporosis, HIV, influenza infection, or any disease not related to the central nervous system or muscles. The specification discloses transgenic mice that express only the heavy or the light chain of the NGF antibody, but discloses no phenotypic characteristics of these mice.

The prior art taught that the production of transgenic animals with desired characteristics is highly unpredictable. The instant invention relies upon expression of an antibody against an endogenous protein e.g. NGF, to approximate the effect of eliminating the expression of that protein. As such, the instant invention is similar to a "knock out" transgenic animal in which a gene of interest has been disrupted. However, at the time of the invention, the phenotype of mice in which expression of targeted genes is reduced was not considered to be predictable. This is apparent from numerous reports. For example, Kappel et al (Curr. Opin. Biol. 3: 548-553, 1992) teach that knock outs of beta2 microglobulin, interleukin 2, interleukin 4, and CD38 were expected to cause severe immuno-incompetence, but this phenotype was not observed

in the actual animals. Furthermore, although early developmental lethality was expected for knockouts of src, homozygous src -/- null animals can survive for at least 5 months, and no detrimental effects were observed in the tissues where src expression is highest. Kappel teaches that this unpredictability may be due to developmental plasticity in an organism, otherwise described as the ability of an animal to compensate for one defect through the use of alternative genes or pathways. See paragraph bridging pages 549 and 550, and first three paragraphs on page 550. Melton (BioEssays 16(9): 633-638, 9/1994) summarizes the use of knockout mice to dissect the genetic organization of muscular development. Contrary to expectations, it was found that mice comprising myoD knockouts possessed muscle and developed normally. Furthermore, myoD null mice had unexpected changes in the expression of myf-5, and myf-5 null mice had changes in the expression of myoD. See last paragraph on page 635 and first paragraph on page 636. Moreadith (J Mol. Med. 75:208-216, 3/1997) teaches that with respect to ideas of gene function, "in many instances [knockouts] have changed the prevailing notions. For example, gene targeting at the endothelin loci subsequently led to the creation of mice with Hirschsprung's disease (aganglionic mega colon) instead of the anticipated phenotype (abnormal control of blood pressure). Indeed if one had even predicted that these mice would survive the absence of a cellular gene that is so widely expressed, one might have been in the minority!" Moreadith goes on to discuss the effects of knocking out the HPRT gene in mice in order to generate a model of Lesch-Nyhan syndrome, noting that the resulting mice had no readily apparent neurological defect. See page 210, column 2, lines 28-34. These

teachings, taken together, illustrate the unpredictable nature of knockout mouse phenotypes, and suggest that this is due to the fact that gene interactions are generally poorly understood, as are the potential compensatory actions which are available to the subject animals.

With respect to the breadth of antibody transgenes and disease phenotypes embraced by the claims, the specification provides no correlation between any antibody and any disease phenotype other than the anti-NGF phenotype and the various neurological and muscular defects listed in the statement of the rejection. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of antibodies and correlating pathologies is a critical element of the invention that cannot be overlooked in the process of providing an enabling disclosure.

With regard to the scope of transgenic animals embraced by the claims, compared with that exemplified in the specification, the level of skill in the transgenic art is such that one cannot predict whether a transgenic phenotype obtained in a mouse will also be obtained in another animal, even if that animal carries a similar transgene construct. Mullins et al (J. Clin. Invest. (1996) 98(11), Supplement S37-S40) taught that position effects can cause loss of cell specificity of expression, overexpression, or silencing of the transgene, and that a given construct may react very differently from one animal to another. See page S37, lines 7-12, and page S39, first sentence of first paragraph. Furthermore, Ebert et al (Mol. Endocrinol. 2(3) : 277-283, 1988) disclosed the production of transgenic mice expressing human somatotropin regulated by the mouse metallothionein promoter at levels sufficient to cause an increase in growth; however, expression of the same transgene in pigs did not produce pigs exhibiting the same phenotypic result (page 277, Introduction, column 2). Also, Hammer et al (J. Anim. Sci. 63 : 269-278, 1986), disclosed the production of transgenic mice, sheep and pigs expressing human growth hormone, however only mice exhibited an increase in growth due to the expression of the transgene (pages 276-277, Subsection: (Effect of Foreign GH on Growth). The inability to extrapolate phenotypes observed in mice to other animals is the result of a variety of unpredictable factors including, for example, the site of integration and methylation-inactivation of the transgene. See Kappel et al (1992), right column of page 549. Also, Wall (Theriogenology 45: 57-68, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements and may result in a lack of transgene

expression or variable expression (paragraph bridging pages 61-62). The nature of the chromatin at the site of insertion can control the expression of the transgene with respect to developmental timing, tissue specificity, and frequency of transcription initiation. These position effects vary with the site of integration, which is totally unpredictable.

With regard to mice expressing fragments of antibodies, the specification discloses two lines of mice that are transgenic for either the heavy or light chain of an anti-NGF antibody. These mice have no disclosed phenotypic characteristics that are reminiscent of a human pathology, and the specification provides no further guidance as to how to make a mouse that expresses a fragment of an antibody and has a pathological phenotype. As discussed above, the court has found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. In view of the available evidence, an entire, functioning anti-NGF antibody is required to produce the exemplified phenotype. Because the specification fails to teach how to make any mouse with any pathological phenotype as a result of expressing less than all of an anti-NGF antibody, there is a failure to meet the enablement requirement.

In view of the art-recognized unpredictability of transgenic animal phenotypes, the unpredictability associated with transgene expression, the inability to predictably obtain similar phenotypes in different species, the failure of the specification to provide the guidance that is missing from the prior art in those regards, as well as the failure of

the specification to provide any correlation between any pathology and any antibody transgene other than anti-NGF, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruberti et al (J. Neurosci 20(7): 2589-2601, 4/2000), as evidenced by Ruberti et al (Cell. Mol. Endocrinol. 13(5): 559-568, 1993).

Ruberti taught a B6SJL mouse transgenic for a chimeric, humanized alphaD11 monoclonal antibody against NGF. See abstract, and paragraph bridging pages 2589 and 2590. Evidence that the antibody is a humanized chimeric antibody is found in the abstract of Ruberti et al (1993), referred to by Ruberti (2000) at the first sentence of paragraph bridging pages 2589 and 2590. Phenotypic characteristics of the mice included expression of the antibody primarily in adulthood, reduced cholinergic neurons in adults but not early postnatal mice, as well as atrophy of skeletal muscles in adult but not post-natal mice. See abstract. The limitations of claim 9 are considered to be met

inasmuch as the muscular atrophy occurred at the same time as the reduction in cholinergic neurons, i.e. in the adult.

It is noted that the three inventors of the instant application are authors of the Ruberti et al reference. However, the reference also cites six other authors not currently listed as inventors. As such, the invention was known or used by another in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. See MPEP 2132 which states:

> The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use.

Thus Ruberti anticipates the claims.

Claims 1-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Capsoni et al (J. Neuroscience Res. 59:553-560, 2/2000).

Capsoni taught a B6SJL mouse transgenic for a chimeric, humanized alphaD11 monoclonal antibody against NGF. See abstract, paragraph bridging pages 553 and 554, and first full paragraph on page 554. The phenotype of the animals includes muscular atrophy, myositis, shrinkage of cholinergic neurons, and reduced clustering of acetylcholine receptors. See abstract; sentence bridging pages 555 and 556; paragraph bridging columns 1 and 2 on page 559, and first full paragraph of column 2 on page 559. This is considered to be reminiscent of human pathologies such as Alzheimer's and muscular dystrophy. Claim limitations not specifically disclosed by Capsoni are

considered to be inherent in the mouse of Capsoni because its genetic structure is indistinguishable from that of the claimed mouse, and the phenotypic characteristics necessarily flow from the genetic structure. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

It is noted that the three inventors of the instant application are authors of the Capsoni et al reference. However, the reference also cites a fourth author who is not currently listed as an inventor. As such, the invention was known or used by another in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. See MPEP 2132 which states:

> The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use.

Thus Capsoni anticipates the claims.

Claims 1-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Capsoni et al (Proc. Nat. Acad. Sci. USA 97(12): 626-6830, 2000) as evidenced by Ruberti et al (J. Neurosci 20(7): 2589-2601, 4/2000).

Capsoni taught a mouse transgenic for a chimeric, humanized alphaD11 monoclonal antibody against NGF. It is clear that the mouse is a B6SJL mouse because Capsoni refers to Ruberti (2000) for details on construction of the mouse, and Ruberti discloses a B6SJL mouse that expresses the anti-NGF antibody. The mouse has a phenotype consistent with Alzheimer-like neurodegeneration, including amyloid plaques, hyperphosphorylated tau, neurofibrillary tangles in cortical and hippocampal neurons, ventricle dilation, cortical and hippocampal atrophy, cholinergic deficit in the forebrain , dystrophic neurites, and spatial memory and object recognition impairments. See entire document.

Claims 1-3, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Piccioli et al (Neuron 15: 373-384, 1995).

Piccioli taught a transgenic mouse expressing a monoclonal antibody against substance P. The phenotype of the animals includes motor deficits. This is considered to be reminiscent of human pathologies such as Alzheimer's and muscular dystrophy.

Thus Piccioli anticipates the claims.

Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Cattaneo et al (Society for Neuroscience Abstracts 22 (1-3): 753, 1996).

Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of mouse monoclonal antibody against NGF joined to human constant regions, under the control of a CMV early promoter. Antibody was expressed at 50-100 ng/ml in adult mice. The mice show a 30% reduction in neurons of the superior cervical ganglia. This phenotypic characteristic is considered to be reminiscent of neurodegenerative diseases. Claim limitations not specifically disclosed by Cattaneo are considered to be inherent in the mouse of Cattaneo because its genetic structure is indistinguishable from that of the claimed mouse, and the phenotypic characteristics necessarily flow from the genetic structure. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cattaneo et al in view of Hogan et al (In *Manipulating the Mouse Embryo,* Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pg 81, 1986).

Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of mouse monoclonal antibody joined to human constant regions, under the control of a CMV early promoter. The mouse was made by injection of a transgene into a fertilized egg (zygote). Cattaneo was silent as to the strain of mouse zygote used to construct the transgenic animal.

Hogan taught that there was a variety of mouse hybrid zygotes that were suitable for the formation of transgenic mice, including hybrids of C57BL/6J and SJL mice, i.e. B6SJL zygotes. See page 81.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the B6SJL hybrid zygotes of Hogan to make the transgenic mice of Cattaneo because Hogan indicated that these zygotes were among several types of zygotes routinely used for the purpose of making transgenic animals. The selection of a particular zygote were among several suitable types is merely a matter of design choice

and, absent case specific indications to the contrary, the zygotes available for use can be viewed as art-recognized equivalents.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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